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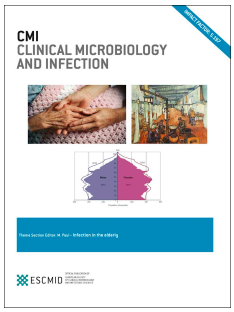

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Commentary – Clinical Microbiology and Infection

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The use of rifampin in staphylococcal orthopaedic-device related infections

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In this issue of *Clinical Microbiology and Infection*, Rieg et al. [1] report on the role of combination therapy in patients with *Staphylococcus aureus* bacteraemia. In patients with implanted devices, they observed less late complications related to *S.aureus* bacteraemia with combination therapy (4.5% [9/202]) than with monotherapy (10.6% [15/142], p=0.03). Most of the patients in the former group were treated with a rifampin combination. These results trigger the discussion on rifampin in orthopaedic-device related infections (ODRIs). In this commentary, we discuss three frequently asked questions. First, should rifampin be added to the anti-staphylococcal treatment in patients with orthopaedic implants and *S.aureus* bacteraemia? Second, at which time should rifampin be started in patients with established ODRI after debridement or replacement surgery? Third, what is the optimal rifampin dose in ODRI? Because it is unlikely that randomized controlled trials investigating these questions will be performed, our viewpoints are presented here.

Several studies have shown a high seeding rate to orthopaedic devices following community-acquired *S.aureus* bacteraemia, ranging from 30% to 40%. In contrast, the risk of ODRI is markedly lower following hospital-acquired *S.aureus* bacteraemia [2]. This points towards the importance of early anti-staphylococcal treatment, since the duration of bacteraemia prior to antimicrobial treatment is generally longer in community-acquired than in hospital-acquired sepsis. Asymptomatic haematogenous seeding to an implant may already have occurred when a patient with community-acquired *S.aureus* bacteraemia is seeking for medical help. If patients with occult ODRI are treated with rifampin combinations for *S.aureus* bacteraemia, the clinical diagnosis may be delayed without elimination of the biofilm infection. Therefore, we do not recommend routine adjunctive rifampin treatment in

patients with *S. aureus* bacteraemia. Since rapid detection and surgical debridement is needed to cure ODRI with implant retention [3], delayed diagnosis should be avoided. Therefore, after *S.aureus* bacteraemia, body sites with orthopaedic devices must be carefully and repeatedly examined for clinical signs of infection. Upon suspicion of ODRI, rapid diagnostic work-up is required.

The optimal time point for starting rifampin therapy in patients with staphylococcal ODRI is still a matter of debate between physicians prescribing it early in the treatment course (i.e., immediately after surgery), and those recommending a delayed treatment start (i.e., after all drains have been removed and the wound is dry). Choosing the optimal time for starting the antibiofilm treatment with rifampin is particularly important in patients with acute ODRI treated either with debridement and implant retention or one-stage exchange. There are several arguments for starting rifampin treatment early. After initial attachment of staphylococci to foreign body surfaces, the process of biofilm formation via cell-cell adhesion and matrix elaboration starts. *In-vitro* studies have shown, that this process is initiated within a short period of time after surface contact [4]. Taking in account that minimal biofilm eradication concentrations (MBECs, also called biofilm MBC) of bacteria are considerably higher than their corresponding minimal inhibitory concentrations (MICs), and that rifampin has good activity on susceptible biofilm staphylococci [5], early start of rifampin after bacterial adhesion to the implant may be advantageous. Nonetheless, we prefer not to start rifampin in the early course of infection, for the following reasons. First, the use of rifampin is endangered by emergence of rifampin resistance. The risk is highest, when administrating rifampin either as monotherapy or to an infectious focus containing a high bacterial load [6]. In the same line of reasoning, the newly published guidelines for staphylococcal

prosthetic valve endocarditis recommends the delay of rifampin treatment until blood cultures have turned negative [7]. Similarly, in orthopaedic surgery, the upcoming course of additional interventions (e.g., removal of haematoma, second look surgery because of persistent wound secretion) is difficult to estimate shortly after the first surgery. In early postoperative period, the bacterial load is unpredictable, but probably still high in case of debridement and implant retention. Second, rifampin penetrates well into all body fluids. Therefore, the skin microbiome is rapidly modified by antimicrobial therapy, and it is conceivable that patients treated with rifampin will select rifampin-resistant staphylococci [8]. Drainages in close proximity of the device and oozing wounds may therefore facilitate exogenous superinfection by rifampin-resistant staphylococci from the skin microbiome. For these arguments, in patients with staphylococcal ODRI, we do not administer rifampin before all drains are removed, the wound is dry, and the bacterial load is lowered by debridement surgery and initial antimicrobial therapy with a standard iv-regimen (e.g., 3 – 5 days after surgery). A retrospective multicentre search for rifampin-resistant staphylococci causing PJI revealed that 44 of 48 cases had a previous episode of PJI, and 93 % of these had been treated with rifampin. This case-control study demonstrates that starting rifampin therapy when bacterial load is still high, and multiple previous surgical revisions are independent risk factors for developing a secondary PJI with rifampin-resistant staphylococci [9]. These observations suggest that the previously raised concern of early rifampin treatment regarding the possible emergence of resistance should be avoided.

In different clinical studies, various doses and/or intervals of rifampin have been used, namely 900 mg once daily, 450 mg twice daily, 600 mg once daily, or 300mg twice daily. In a neutropenic murine infection model with *S.aureus* isolates,

PK/PD indexes which best predict rifampin efficacy are a concentration-dependent killing (C_{max}/MIC) and the area under the curve (AUC)/MIC [10]. Furthermore, rifampin has a long post-antibiotic effect in a *S. aureus* biofilm infection mouse model [11]. The $AUC_{0\text{-}24h}$ between 900 mg once daily and 450 mg twice daily does likely not significantly influence the AUC/MIC ratio. Though, in our experience, 450 mg twice daily is better tolerated than 900 mg once daily. This in particular important when considering that in ODRI the compound is commonly administered for 6 to 12 weeks or even longer. It is uncertain, whether once or twice daily dosing matters after a steady state has reached, since all of the above mentioned regimens have shown clinical efficacy. In our view, it is clinically useful to start treatment at high dose (e.g., 450 mg twice daily), and reduce the dose in case of intolerance. Severe nausea, frequently occurring in the elderly, does not respond to antiemetic drugs. In a trial on the role of rifampicin in staphylococcal ODRI, severe nausea was observed in 17% of the patients treated with 450 mg twice daily [3]. In these patients, rifampin therapy could be continued after temporary stop with a reduced dose of 300 mg twice daily, indicating that these adverse events are – as observed in patients with anti-tuberculous treatment – dose dependent.

In contrast to the $AUC_{0\text{-}24h,}$ C_{max} likely differs between once and twice daily regimens. However, even when considering C_{max}/MIC or C_{max}/MBEC as efficacy variable, there are *in vitro* arguments and mathematical extrapolations supporting that 300 mg twice daily may be as efficient as 600 mg once daily. C_{max} in adults with tuberculosis treated with 300 mg rifampin once daily is approximately 6.6 (range 2.9 – 14) µg/mL [12]. In six elderly male nursing home residents who received 300 mg rifampin orally every 12 hours for 14 days (in addition to ciprofloxacin), C_{max} after dose 12 and 27 were 9.4 ± 3.1 and 7.3 ± 2.3 µg/mL, respectively [13]. Rifampin

bone/serum concentration ratios of 0.2–0.5 are found in humans (reviewed in [14]). Thus, calculated C_{max} in bone are 1.3 – 4.5 µg/mL (range of medians, total range 0.6 – 6) µg/mL. Though, this calculation does not take into account the accumulation in bone, since distribution in and elimination from various comportments is not linear [15]. Nonetheless, most staphylococci have a MIC for rifampin of ≤0.064 µg/mL. There is no uniformly accepted microbiological method for determining MBECs. Many 'biofilm' staphylococci have a minimal bactericidal concentration of ≤2 µg/mL, and in combination with another compound, rifampin is active against the majority of these isolates [5]. Thus, it is likely that bone levels of rifampin with 300 mg twice daily are high enough to potentially cure the infection. Therefore, we recommend a delayed treatment start of adjunctive rifampin in staphylococcal ODRI with 450 mg twice daily; in case of intolerance, we recommend reducing the dose to 300 mg twice daily.

Transparency declaration

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